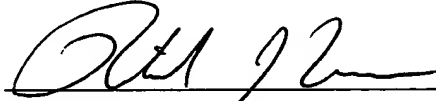


REMARKS

The above amendments correct obvious errors and do not add new matter.

Respectfully submitted,



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Filed: December 12, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Paragraph beginning at page 5, line 21 has been amended as follows:

R_z is preferably hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 ~~heteroatom~~ heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C_{3-C12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C_{6-C14} aryl, substituted C_{3-C10} cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from S, N and O, substituted C₇₋₂₄ alkaryl or substituted C_{7-C24} aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_{3-C12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g,

Please replace the paragraph beginning at page 6, lines 3, 7, 19, 20 and 25, with the following rewritten paragraph:

--up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g, wherein R_g is as defined below

R_a and R_b preferably are,

a) independently hydrogen,

a carbon based moiety selected from ~~to~~ the group consisting of C_{1-C10} alkyl, C_{1-C10} alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C_{7-C24} alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N,

S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g wherein R_g is as defined below; or

-OSi(R_f)₃ where R_f is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, S and N, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, substituted C₃₋₁₂ ~~heteraryl~~ hetaryl having 1-3 heteroatoms selected from O, S, and N, substituted C₆₋₁₂ aryl, and substituted C₇₋₂₄ alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3--

Please replace the paragraph beginning at page 7, lines 2, 3, 13-14 and 26-27 with the following paragraph:

-- heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g wherein R_g is as defined below,

or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, halo substituted C₁₋₆ alkyl up to per halo alkyl, halo substituted C₆₋₁₂ aryl up to per halo aryl, halo substituted C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C₇₋₂₄ aralkyl up

to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,
wherein R_g is as defined below,

or

c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members,

wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆-C₁₂ halo substituted aryl up to per halo aryl, C₃-C₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃-C₁₂ hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C₇-C₂₄ aralkyl up to per halo aralkyl, halo substituted C₇-C₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g, wherein R_g is as defined below,--

Please replace the paragraph beginning at page 9, line 17, with the following paragraph:

-- Z is preferably independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₂-C₁₀ alkenyl, C₁-C₁₀ alkenoyl, C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkoxy, substituted C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkenoyl, substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C₆-C₁₂ aryl, substituted C₇-C₂₄ alkaryl, substituted C₇-C₂₄ aralkyl and substituted C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷, wherein R⁷ is as defined above.

M is preferably one or more bridging groups selected from the group consisting of -O-

, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, -CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined in claim 1 above.

Please replace the paragraph beginning at page 11, lines 11 and 12, with the following paragraph:

-- The present invention is also directed to pharmaceutically acceptable salts of formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, ~~sulphuric~~ sulfuric acid, phosphoric acid, ~~methanesulphonic~~ methanesulfonic acid, trifluoromethanesulfonic acid, ~~benzenesulphonic~~ benzenesulfonic acid, *p*-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺ Na⁺ or K⁺), alkaline earth cations (e.g., Mg⁺², Ca⁺² or Ba⁺²), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).--

Please replace the paragraph beginning at page 12, line 12, with the following paragraph:

----Substituted and unsubstituted aminoquinolines, aminoisoquinolines and aminopyridines may be prepared using standard methods (see, for example: A.R. ~~Katritzky~~ Katritsky et al. (Eds.). *Comprehensive Heterocyclic Chemistry II*, Vol. 5. M.H. Palmer. *Heterocyclic Compounds*; Arnold Ltd., London (1967). C.K. Esser et al. WO 96/18616. C.J. Donahue et al. *Inorg. Chem.* **30**, 1991, 1588. E. Cho et al. WO 98/00402. A. Cordi et al. *Bioorg. Med. Chem.* **3**, 1995, 129). In addition, many aminoquinolines, aminoisoquinolines and aminopyridines are commercially available.--

Please replace the paragraph beginning at page 20, line 31, with the following paragraph:

--It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, ~~teh~~ the gender of the patient, the diet of the patient, time of--

Please replace the paragraph beginning at page 21, lines 3 and 15, with the following paragraph:

-- administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, ~~ie.~~, i.e. the mode of treatment and the daily number of doses of a compound of Formula I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.--

The compounds of ~~Figure~~ Formula I are producible from known compounds (or from starting materials which, in turn, are producible from known compounds), e.g., through the general preparative methods shown below. The activity of a given compound to inhibit raf kinase can be routinely assayed, e.g., according to procedures disclosed below. The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.--

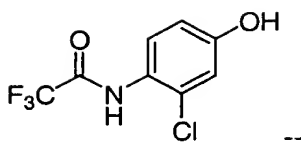
Please replace the paragraph beginning at page 23, line 3, with the following paragraph:

-- Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared ~~spreetra~~ spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (¹H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ0.00) or

residual protonated solvent (CHCl_3 δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl_3 δ 77.0; MeOD-d_3 δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250 °C. Electron impact ionization was performed with electron energy of 70 eV and a trap current of 300 μA . Liquid-caesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment were obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas (1×10^{-4} torr to 2.5×10^{-4} torr). The direct insertion desorption chemical ionization (DCI) probe (Vacumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microlit Labs, Madison NJ.--

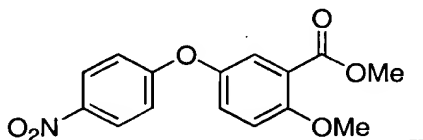
Please replace the paragraph beginning at page 24, line 2, with the following paragraph:
 -- All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS ~~consistent~~ consistent with assigned structures.--

Please replace the paragraph beginning at page 33, line 17, with the following paragraph:
 -- A6. **General Method for the Synthesis of Anilines from Hydroxyanilines by N-Protection, Nucleophilic ~~Aromatic~~ Aromatic Substitution and Deprotection. Synthesis of 4-(2-(N-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline**



Please replace the paragraph beginning at page 35, line 19, with the following paragraph:

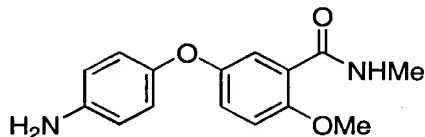
- A8. **General Method for Synthesis of ω -Alkoxy- ω -carboxyphenyl Anilines.**
Synthesis of 4-(3-(~~N-Methylearbamoyl~~ N-Methylcarbamoyl)-4-methoxyphenoxy)aniline.



Please replace the paragraph beginning at page 36, lines 14, 23 and 25, with the following paragraph:

- Step 3. **4-(3-(~~N-Methylearbamoyl~~ N-Methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene:**

To a solution of 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (0.50 g, 1.75 mmol) in CH_2Cl_2 (12 mL) was added SOCl_2 (0.64 mL, 8.77 mmol) in portions. The resulting solution was heated at the reflux temp. for 18 h, cooled to room temp., and concentrated under reduced pressure. The resulting yellow solids were dissolved in CH_2Cl_2 (3 mL) then the resulting solution was treated with a methylamine solution (2.0 M in THF, 3.5 mL, 7.02 mmol) in portions (CAUTION: gas evolution), and stirred at room temp. for 4 h. The resulting mixture was treated with a 1N NaOH solution, then extracted with CH_2Cl_2 (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give 4-(3-(~~N-methylearbamoyl~~ N-methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene as a yellow solid (0.50 g, 95%).



- Step 4. 4-(3-(~~N-Methylearbamoyl~~ N-Methylcarbamoyl)-4-methoxyphenoxy)aniline:--**

Please replace the paragraph beginning at page 45, line 10, with the following paragraph:

- Step 1. **4-Chloro-N-(2-triisopropylsilyloxy)ethylpyridine-2-carboxamide**

To a solution of 4-chloro-*N*-(2-hydroxyethyl)pyridine-2-carboxamide (prepared in a manner analogous to Method A2, Step 3b; 1.5 g, 7.4 mmol) in anhyd DMF (7 mL) was added triisopropylsilyl chloride (1.59 g, 8.2 mmol, 1.1 equiv.) and imidazole (1.12 g, 16.4 mmol, 2.2 equiv.). The resulting yellow solution was stirred for 3 h at room temp, then was concentrated under reduced pressure. The residue was separated between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (MgSO₄), and concentrated under reduced pressure to afford 4-chloro-2-(*N*-(2-triisopropylsilyloxy)ethyl)pyridinecarboxamide as an orange oil (2.32 g, 88%). This material was ~~used~~ used in the next step without further purification.--

Please replace the paragraph beginning at page 46, line 10, with the following paragraph:
-- A mixture of 5-hydroxy-2-methylpyridine (10.0 g, 91.6 mmol), 1-fluoro-4-nitrobenzene (9.8 mL, 91.6 mmol, 1.0 equiv), K₂CO₃ (25 g, 183 mmol, 2.0 equiv) in DMF (100 mL) was heated at the reflux temperature overnight. The resulting mixture was cooled to room temperature, treated with water (200 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were sequentially washed with water (2 x 100 mL) and a saturated NaCl solution ((100 mL), dried (MgSO₄), and concentrated under reduced pressure to give 4-(5-(2-methyl)pyridyloxy)-1-nitrobenzene as ~~abrown~~ a brown solid (12.3 g).--

Please replace the paragraph beginning at page 47, lines 9 and 21, with the following paragraph:

-- **A18 A19. Synthesis of ω -Sulfonylphenyl Anilines. Synthesis of 4-(4-Methylsulfonylphenoxy)aniline.--**

-- **Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline:** 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner ~~analogous~~ analogous to that described in Method A17, step 3.--

Please replace the paragraph beginning at page 54, line 23, with the following paragraph:

-- A solution of 4-*tert*-butyl-2-aminopyridine (0.177 g, 1.18 mmol, 1 equiv.) in 1.2 mL of anhyd. CH₂Cl₂ (1.2 mL) was added to CDI (0.200 g, 1.24 mmol, 1.05 equiv) and the mixture was allowed ~~allowed~~ to stir under argon at room temperature 1 d. To the resulting solution was added 4-(4-chlorophenoxy)aniline (0.259 g, 1.18 mmol, 1 equiv.) in one portion. The

was added 4-(4-chlorophenoxy)aniline (0.259 g, 1.18 mmol, 1 equiv.) in one portion. The resulting mixture was stirred at room temperature for 1 d, then was treated with a 10% citric acid solution (2 mL) and allowed to stir for 1 h. The resulting organic layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The resultant residue was treated with CH₂Cl₂ (10 mL) and a 1 N aqueous NaOH solution. This mixture was allowed to stir overnight. The resulting organic layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were (MgSO₄) and concentrated *in vacuo*. The resultant solids were suspended in diethyl ether (10 mL) and sonicated for 15 minutes. The resulting white solid were dried to give *N*-(4-*tert*-butylpyridyl)-*N'*-(4-(4-chlorophenoxy)phenyl) urea (42 mg, 9%): mp 198-199 °C.--

Please replace the paragraph beginning at page 55, lines 6 and 17, with the following paragraph:

-- resulting mixture was stirred at room temperature for 1 d, then was treated with a 10% citric acid solution (2 mL) and allowed to stir for 1 h. The resulting organic layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The resultant residue was treated with CH₂Cl₂ (10 mL) and a 1 N aqueous NaOH solution. This mixture was allowed to stir overnight. The resulting organic layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The resultant solids were suspended in diethyl ether (10 mL) and sonicated for 15 minutes. The resulting white solid were dried to give *N*-(4-*tert*-butylpyridyl)-*N'*-(4-(4-chlorophenoxy)phenyl) urea (42 mg, 9%): mp 198-199 °C.

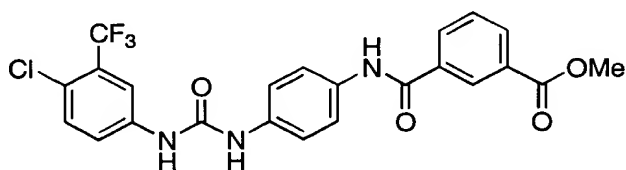
One of the anilines to be coupled was dissolved in dichloroethane (0.10 M). This solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this was added a bis(trichloromethyl) carbonate solution (0.12 M in dichloroethane, 0.2 mL, 0.4 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The vial was capped and ~~heat~~ heated at 80 °C for 5 h, then allowed to cool to room temp for approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5 mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The resulting mixture was heated at 80 °C for 4 h, cooled to room temperature and treated with MeOH (0.5 mL). The resulting mixture was concentrated under reduced pressure and the products were purified by reverse phase HPLC.--

Please replace the paragraph beginning at page 56, lines 8 and 10, with the following paragraph:

-- To a stirring solution of phosgene (1.9 M in toluene; 2.07 mL 0.21 g, 1.30 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added anhydrous pyridine (0.32 mL) followed by 2-methoxy-5-(trifluoromethyl)aniline (0.75 g). The yellow solution was allowed to warm to room temperature during which a precipitate formed. The yellow mixture was stirred for 1 h, then concentrated under reduced pressure. The resulting solids were treated with anhydrous toluene (20 mL) followed by 4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)aniline (prepared as described in Method A2; 0.30 g) and the resulting suspension was heated at 80 °C for 20 h, then allowed to cool to room temperature. The ~~resulting~~ resulting mixture was diluted with water (100 mL), then was made basic with a saturated NaHCO₃ solution (2-3 mL). The basic solution was extracted with EtOAc (2 x 250 mL). The organic layers were ~~separately~~ separately washed with a saturated NaCl solution, combined, dried (MgSO₄), and concentrated under reduced pressure. The resulting pink-brown residue was dissolved in MeOH and absorbed onto SiO₂ (100 g). Column chromatography (300 g SiO₂; gradient from 1% Et₃N/33% EtOAc/66% hexane to 1% Et₃N/99% EtOAc to 1% Et₃N/20% MeOH/79% EtOAc) followed by concentration under reduced pressure at 45 °C gave a warm concentrated EtOAc solution, which was treated with hexane (10 mL) to slowly form crystals of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea (0.44 g): TLC (1% Et₃N/99% EtOAc) R_f 0.40.--

Please replace the paragraph beginning at page 57, line 14, with the following paragraph:

- **D. Interconversion of Ureas**
- D1a. Conversion of ω-Aminophenyl Ureas into ω-(Arylamino Arylamino)phenyl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) Urea**



Please replace the paragraph beginning at page 60, line 20, with the following paragraph:

-- *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-methoxycarbonylpyridyl)oxyphenyl) urea was synthesized from 4-chloro-3-(trifluoromethyl)phenyl isocyanate and 4-(3-(5-methoxycarbonylpyridyl)oxyaniline (Method A14, Step 2) in a manner analogous to Method C1a. A suspension of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-methoxycarbonylpyridyl)oxyphenyl) urea (0.26 g, 0.56 mmol) in MeOH (10 mL) was treated with a solution of KOH (0.14 g, 2.5 mmol) in water (1 mL) and was stirred at room temp. for 1 h. The resulting mixture was adjusted to pH 5 with a 1 N HCl solution. ~~The~~ The resulting ~~preecipitate~~ precipitate was removed by filtration and washed with water. The resulting solids were dissolved in EtOH (10 mL) and the resulting solution was concentrated under reduced pressure. The EtOH/concentration procedure was repeated twice to give *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-((4-(3-(5-carboxypyridyl)oxyphenyl) urea (0.18 g, 71%).--

Please replace the paragraph beginning at page 61, line 24, with the following paragraph:

-- To a solution of *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-triisopropylsilyloxy)ethylcarbamoyl)pyridyloxyphenyl) urea (prepared in a manner analogous to Method C1a; 0.25 g, 0.37 mmol) in anh THF (2 mL) was tetrabutylammonium fluoride (1.0 M in THF; 2 mL). The mixture was stirred at room temperature for 5 min, then was treated with water (10 mL). The aqueous mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (MgSO₄) and ~~eeinecentrated~~ concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; gradient from 100% hexane to 40% EtOAc/60% hexane) to give *N*-(4-chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(4-(2-(*N*-(2-hydroxy)ethylcarbamoyl)pyridyloxyphenyl) urea as a white solid (0.019 g, 10%).--

Please replace the paragraph beginning at page 64, line 18, with the following paragraph:

-- Entry 15: According to Method C2d, 5-(~~triflouromethyl~~ trifluoromethyl)-2-methoxyaniline was reacted with CDI followed by 4-(3-*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had been prepared according to Method A8, to afford the urea.--

Please replace the paragraph beginning at page 65, line 27, with the following paragraph:

-- Entry 21: 4-(4-Methylthiophenoxy)-1-nitrobenzene was oxidized according to Method

~~A18~~ A19, Step 1 to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene. The nitrobenzene was reduced according to Method ~~A18~~ A19, Step 2 to give 4-(4-methylsulfonylphenoxy)-1-aniline. According to Method C1a, 5-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(4-methylsulfonylphenoxy)-1-aniline to afford the urea.--

Please replace the paragraph beginning at page 72, line 17, with the following paragraph:
-- Entry 53: 4-(4-Methylthiophenoxy)-1-nitrobenzene was oxidized according to Method ~~A18~~ A19, Step 1 to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene. The nitrobenzene was reduced according to Method A18, Step 2 to give 4-(4-methylsulfonylphenoxy)-1-aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-methylsulfonylphenoxy)-1-aniline afford the urea.--

Please replace the paragraph beginning at page 76, line 28, with the following paragraph:
-- Entry 71: 4-(3-(5-Methoxycarbonyl)pyridyloxy)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyloxy)aniline according to Method C1a to afford the urea. *N*-(4-Chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(3-(5-methoxycarbonylpyridyl)oxy)phenyl) urea was saponified according to Method ~~D4~~ D4, Step 1, and the corresponding acid was coupled with 4-(2-aminoethyl)morpholine to afford the amide.

IN THE CLAIMS

Claims 2, 3, 5, 8, 10, 25 and 26 have been amended as follows.

2. (Amended) A compound as in claim 1 wherein:

R_y is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₄ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ alkaryl or substituted C₇₋₂₄ aralkyl, where R_y is a substituted group, it is substituted by halogen up to per halo,

R_z is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatom, C₂₋₁₀

alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C_{3-C12} hetaryl having 1-3 heteroatoms selected from S, N and O, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C_{6-C14} aryl, substituted C_{3-C10} cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from S, N and O, substituted C₇₋₂₄ alkaryl or substituted C_{7-C24} aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo ~~substituted~~ substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g,

R_a and R_b are,

a) independently hydrogen,

a carbon based moiety selected from the group consisting of C_{1-C10} alkyl, C_{1-C10} alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C_{7-C24} alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_{3-C12} hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g; or

-OSi(R_f)₃ where R_f is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C_{3-C10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₆₋₁₂ aryl, C_{3-C12} hetaryl having 1-3 heteroatoms selected from O, S and N, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C_{1-C10} alkoxy, substituted C_{3-C12} cycloalkyl having 0-3 heteroatoms selected from O, S and N,

substituted C₃-C₁₂ ~~heteraryl~~ hetaryl having 1-3 heteroatoms selected from O, S, and N, substituted C₆₋₁₂ aryl, and substituted C₇₋₂₄ alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo ~~heteraryl~~ hetaryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

or

b) R_a and R_b together from a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, halo substituted C₁₋₆ alkyl up to per halo alkyl, halo substituted C₆₋₁₂ aryl up to per halo aryl, halo substituted C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo heteraryl, halo substituted C₇₋₁₂ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

or

c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members,

wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C₆₋₁₂ halo substituted aryl up to per halo aryl, C₃₋₁₂ halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C₃₋₁₂ hetaryl up to per halo heteraryl, halo substituted C₇₋₂₄ aralkyl up to per halo aralkyl, halo substituted C₇₋₂₄ alkaryl up to per halo alkaryl, and -C(O)R_g,

where R_g is C_{1-10} alkyl; $-CN$, $-CO_2R_d$, $-OR_d$, $-SR_d$, $-NO_2$, $-C(O)R_e$, $-NR_dR_e$, $-NR_dC(O)OR_e$ and $-NR_dC(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7-C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6-C_{14} aryl, up to per halo substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl,

W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_{1-10} alkyl, C_{1-10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N and S, substituted C_7-C_{24} aralkyl, substituted C_7-C_{24} alkaryl, substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and $-Q-Ar$;

each R^7 is independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl ~~having~~ having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_7-C_{24} aralkyl, up to per-halosubstituted C_7-C_{24} alkaryl, and up to per-halosubstituted C_4-C_{23} alkheteroaryl; and

each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$,

-C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₂-C₁₀ alkenyl, C₁-C₁₀ alkenoyl, C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkoxy, substituted C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkenoyl, substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C₆-C₁₂ aryl, substituted C₇-C₂₄ alkaryl, substituted C₇-C₂₄ aralkyl and substituted C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷.

3. (Amended) A compound as in claim 1 wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined in claim 1.

5. (Amended) A compound of claim 1 wherein B of Formula I is a substituted pyridyl, substituted quinoliny or isoquinoliny group substituted 1 to 3 times by 1 or more substituents selected from the group consisting of -CN, halogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, -OH, up to ~~to~~ per halo substituted C₁-C₁₀ alkyl, up to per halo substituted C₁-C₁₀ alkoxy or phenyl substituted by halogen up to per halo.

8. (Amended) A compound of claim 1, wherein said substituted cyclic moiety L¹ comprises a 5 to 6 membered aryl moiety or hetaryl moiety, wherein said ~~heteraryl~~ hetaryl moiety comprises 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulfur.

10. (Amended) A compound of claim 7, wherein said substituted ~~eylie~~ cyclic moiety L¹ is phenyl, pyridinyl or pyrimidinyl.

25. (Amended) A compound of claim 1 which is a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

- a) basic salts of organic acids and inorganic acids selected from the group

consisting of hydrochloric acid, ~~hydrobromic~~ hydrobromic acid, sulphuric acid, phosphoric acid, ~~methanesulphonic~~ methanesulfonic acid, ~~trifluorosulphonic~~ trifluorosulfonic acid, benzenesulfonic acid, p-toluene ~~sulphonic~~ sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, ~~trifluoroacetic~~ trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

- b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

26. (Amended) A compound of claim 20 which is pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

- a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, ~~hydrobromic~~ hydrobromic acid, sulphuric acid, phosphoric acid, ~~methanesulphonic~~ methanesulfonic acid, ~~trifluorosulphonic~~ trifluorosulfonic acid, benzenesulfonic acid, p-toluene ~~sulphonic~~ sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, ~~trifluoroacetic~~ trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and
- b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.